REMARKS/ARGUMENTS

Claims 1-5 and 7-12 are pending in this application after entry of this Amendment. Claim 6 is canceled and claims 1, 3, 4, 5, 8, 9, 11, and 12 are amended herewith, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. No new matter has been added. The claims are amended to clarify the subject matter Applicants regard as their invention. No new matter has been added.

The claims stand rejected under 35 U.S.C. 103(a) as being obviousness over three separate combinations of references.

Rejection of the Claims under 35 U.S.C. § 103(a)

A.) Rejection of Claims 2, 7, and 10 over US 6,093,704 to Nickel et al. ("Nickel 704") , US 6,696,428 to Nickel et al. ("Nickel 428"), and US 6,172,050 to Nössner et al. ("Nössner"), in view of Calabresi et al., Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Ninth Edition ("Calabresi"), as evident by Kasianenko 1998:87 (2 pages) Abstract only ("Kasianenko").

The Nickel 704 patent discloses the use of dopamine receptor antagonists in combination with alkylphosphocholines, particularly miltefosine, to reduce the decrease in body mass that can accompany treatment with alkylphosphocholines.

The Nickel 428 patent also discloses the use of dopamine receptor antagonists in combination with alkylphosphocholines, particularly perifosine, to reduce the decrease in body mass that can accompany treatment with alkylphosphocholines. Neither of the Nickel patents disclose the use of alkylphosphocholines in combination with any antitumor agents.

The Nössner patent discloses the treatment of mammary carcinoma with alkylphosphocholines such as octadecyl-1,1-dimethylpiperidino-4-yl phosphate. This reference compares the activity of the mentioned alkylphosphocholines with standard cytostatics such as cyclophosphamide, cisplatin, and adriamycin (column 19, lines 48-54). However, this reference

does not teach the use of alkylphosphocholines in combination with any antitumor agents for the treatment of tumors.

The Kasianenko reference discloses the treatment of breast cancer's cutaneous manifestations using topical miltefosine. This reference does not teach any combinations of miltefosine with other antitumor agents.

The Calabresi reference teaches that single-agent chemotherapy can lead to the outgrowth of cancer cells that are resistant to the chemotherapeutic (see page 1230). The Calabresi reference further teaches that there are a variety of mechanisms by which tumor cells acquire drug resistance (page 1230, 2nd paragraph), and that drugs are generally more effective in combination and may be synergistic through biochemical interactions. The Calabresi reference explains that in designing drug regimens for clinical use, it is desirable to use drugs that do not share common mechanisms of resistance and that do not overlap in their major toxicities (see page 1230).

The Office action states that the three primary references (Nickel, Nickel, and Nössner), as well as the Kasianenko reference, teach that alkylphosphocholines such as those presently claimed as part of a combination therapy, can be used in the treatment of breast cancer. Although the primary references do not teach the claimed combinations, the Examiner argues that the Calabresi reference teaches that drugs are generally more effective in combination and may be synergistic through biochemical interactions. Essentially, the Examiner's position is that where two different compounds are each useful for the treatment of a particular condition, it flows logically to combine them for the treatment of that same condition. Accordingly, the Office action states that the claimed combination would have been obvious to a person of ordinary skill in the art at the time of the claimed invention.

Applicants respectfully submit that the Examiner has construed the Calabresi reference too narrowly. The Calabresi reference discloses that there are a variety of mechanisms by which tumor cells acquire drug resistance (page 1230, 2nd paragraph). Further, the Calabresi reference discloses that drug resistant cells may be selected from the larger tumor population by exposure to low-dose single agent chemotherapy. The Calabresi reference teaches that combination

cancer chemotherapy is generally more effective because the tumor is less likely to develop an outgrowth of cells that is resistant to both chemotherapeutics. However, as the Calabresi reference makes clear, useful combinations of drugs do not share common mechanisms of resistance, and do not overlap in their major toxicities (page 1230).

It follows that not every combination of drugs will be effective against all types of tumor. Indeed, one may infer from the teaching of the Calabresi reference that two compounds that are individually useful for treating a particular cancer type would not be useful in combination if they share common mechanisms of resistance or if they overlap in their major toxicities. Although the Calabresi reference teaches that a properly selected combination may be useful, it provides no specific direction as to selecting a particular combination for mammary carcinoma, or for any other tumor type. Absent an understanding of the mechanisms of drug resistance and drug activity, one of ordinary skill in the art would have no obvious way of selecting effective combinations of alkylphosphocholines and other antitumor agents. (See the discussion of the Patel reference below, for disclosure that exact mechanisms of action of ALKs were unknown at the time of the invention.) Accordingly, use of the combinations of claims 2, 7, and 10 would not have been obvious to a person of ordinary skill in the art at the time that the claimed invention was made.

At least by virtue of the remarks set forth above, Applicants respectfully submit that claims are patentable over the cited art.

B.) Rejection of Claims 2, 7, and 10 over Hilgard et al. Cancer Chemother. Pharmacol., (1993) 32:90-95 ("Hilgard") in view of Stekar et al. European J. of Cancer, (1995) Vol. 31(3) pp 372-374 ("Stekar").

The Hilgard reference discloses the use of miltefosine in combination with cyclophosphamide for the treatment of mammary carcinoma, and discloses by reference the combination of miltefosine with cisplatin derivatives. This reference does not teach any other combinations.

The Stekar reference discloses the treatment of mammary carcinoma with a two week oral dosing of miltefosine followed by an injection of cyclophosphamide. This reference does not teach any other combinations.

The Office action states that one of ordinary skill in the art would have been motivated to administer miltefosine prior to administration of other antitumor agents because of the disclosure of the Stekar reference. Furthermore, the Office action states that the disclosure of miltefosine in combination with cyclophosphamide as cited in these references would have motivated a person of ordinary skill in the art to use other known antitumor agents in combination with alkylphosphocholines, and would have given the person of ordinary skill in the art a reasonable expectation of success.

Applicants argue that neither the Hilgard reference nor the Stekar reference teach the combinations of the claimed invention. As discussed above with respect to the Calabresi reference, a person of ordinary skill in the art would not be motivated to use each and every combination of antitumor agents based on the teaching of a particular combination. Antitumor agents are highly cytotoxic compounds that have particularized dosing regimens, toxicity profiles, and side effect profiles. Combined use of a particular combination might lead to a synergistically enhanced detrimental side effects, rather than enhanced desireable synergistic activity. Furthermore, because different tumor types have different drug resistance mechanisms, some combinations will not defeat the tumor's drug resistance mechanisms at all. A person of ordinary skill in the art, lacking an understanding of the mechanism of action of ALKs or their drug resistance pathways, would face considerable experimentation with a large number of combinations and no necessary expectation of success. Accordingly, the combinations of the claimed invention would not have been obvious at the time the invention was made.

At least by virtue of the remarks set forth above, Applicants respectfully submit that claims are patentable over the cited art.

C.) Rejection of Claims 1-12 over Hilgard et al. Cancer Chemother. Phamacol, (1993) 32:90-95 ("Hilgard") and Stekar et al. European J. of Cancer, (1995) Vol. 31(3) pp 372-374

("Stekar") in view of US 6,172,050 to Nössner et al. ("Nössner"), further in view of Patel et al., Cancer Research (March 1, 2002), 62, 1401-1409 ("Patel").

The teachings of the Hilgard, Stekar, and Nössner references have been summarized above.

The Patel reference discloses the use of perifosine for the treatment of head and neck small cell carcinoma. The Patel reference further discloses that some tumor cell lines, including breast cancer, have reasonable sensitivity to perifosine. The Patel reference also points to three references that purport to teach that ALKs have synergistic cytotoxic properties with cyclophosphamide, cisplatin, and gamma irradiation. Perhaps most importantly, the Patel reference discloses that the exact mechanism of the antiproliferative properties of ALKs remains unclear (page 1401, column 2), and that the role of ALKs on cell cycle progression is still unknown (page 1406, column 2).

The Office action states that the Nössner reference discloses that compounds of the present invention may be administered in a regimen (column 19, lines 34-35), and that these compounds can be combined with cisplatin, cyclophosphamide (column 19, lines 48-54). The Office action also states that one of ordinary skill in the art would have been motivated by the prior art to combine the above references to arrive at the claimed invention. The Office action cites the Patel reference as teaching that compounds of Formula II demonstrate synergism when combined with other chemotherapeutic agents.

Applicants disagree with the Examiner's position that Nössner discloses that compounds of Formula II can be combined with cisplatin or cyclophosphamide. Lines 48-54 of the Nössner reference read as follows:

> Treating the DMBA-induced mammary carcinomas in test rats and the KB implanted tumors in test mice with standard cytostatics (e.g., Cyclophosphamide, Cisplatin and Adriamycin) proved relatively ineffective. The result demonstrates that the compounds described herein are superior to presently known cytostatics employed clinically in the treatment of tumors.

The Nössner reference is comparing the efficacy of heterocyclic alkylphosphocholines (such as those of Formula II of the present invention) with conventional cytostatics, including cisplatin and cyclophosphamide. The Nössner reference is not describing or advocating the combination of heterocyclic alkylphosphocholines with conventional cytostatics.

Applicants argue that the disclosure in the Nössner reference of specified dosing regimens has no bearing on the patentability of the claimed invention. The regimens described in the Nössner reference correspond to different dosage levels and administration frequencies of single alkylphosphocholines. These regimens do not refer to combinations of alkylphosphocholines with any other chemotherapeutic.

Applicants reiterate the argument presented as to the rejections above. Antitumor agents are highly cytotoxic compounds that have particularized dosing regimens, toxicity profiles, and side effect profiles. Combined use of a particular combination might lead to a synergistically enhanced detrimental side effects, rather than enhanced desirable synergistic activity. Furthermore, because different tumor types have different drug resistance mechanisms, some combinations will not defeat the tumor's drug resistance mechanisms at all. Accordingly, the teaching of a particular combination does not make obvious other combinations.

The teaching of the Patel reference further supports the Applicants' claim of nonobviousness. Because the exact mechanism of action of ALKs was unclear, and because the role of ALKs on the cell cycle progression was unclear, a person of ordinary skill in the art would not have been motivated to combine ALKs with any particular chemotherapeutic agent. In view of the teaching of the Calabresi reference, a person of ordinary skill in the art, lacking an understanding of the mechanism of action of ALKs, would face considerable experimentation with a large number of combinations and no necessary expectation of success. Accordingly, the combinations of the claimed invention would not have been obvious at the time the invention was made.

The Office action also states that claims 7 and 8 would have been obvious to a person of ordinary skill in the art because cyclophosphamide is an antitumor agent with low molecular

weight as required by claim 7, and because cyclophosphamide is a heterocyclic compound as required by claim 8.

As to claim 7, Applicants disagree with the Examiner's reasoning. Claim 7 is directed to combinations of alkylphosphocholines and signal transduction inhibitors that are high and low molecular weight inhibitors of receptor and/or cytosolic kinases. While cyclophosphamide may be considered a low molecular weight compound, cyclophosphamide is not a signal transduction inhibitors of receptor and/or cytosolic kinases. Cyclophosphamide is an alkylating agent that exerts its effect by alkylating DNA (see Calabresi, page 1227). Accordingly, Claim 7 is not rendered obvious by a disclosure of alkylphosphocholines in combination with cyclophosphamide.

Claim 8 is directed to a combination of alkylphosphocholines of Formula II and monoclonal antibodies or heterocyclic compounds. Claim 8 has been amended with a proviso that the heterocyclic compound can not be cyclophosphamide. Accordingly, Claim 8 is not rendered obvious by a disclosure of alkylphosphocholines in combination with cyclophosphamide.

At least by virtue of the remarks set forth above, Applicants respectfully submit that claims are patentable over the cited art.

Additional Art of Record

Applicants kindly bring the Examiner's attention to Hilgard et al., "Heterocyclic Phospholipids with an Improved Therapeutic Range; Advances in Experimental Medicine and Biology, United States (1996), 157-164 ("the Hilgard publication"), which is already of record. Applicants respectfully submit that the pending claims are also patentable over the Hilgard publication, which does not disclose any of the combinations in the claims, as amended .

CONCLUSION

Based on the foregoing amendments and remarks, favorable consideration and allowance of all of the claims now present in the application are respectfully requested.

Should the Examiner require or consider it advisable that the specification, claims and/or drawings be further amended or corrected in formal respects in order to place the case in condition for final allowance, then it is respectfully requested that such amendment or correction be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing this case to allowance, the Examiner is invited to telephone the undersigned.

The Commissioner is authorized to charge any required fees, including any extension and/or excess claim fees, any additional fees, or credit any overpayment, to Goodwin Procter LLP Deposit Account No. 06-0923.

Respectfully submitted for Applicants,

Timothy Doyle (Reg. No. 58,127)
GOODWIN PROCTER LLP
599 Lexington Avenue
New York, NY 10022
(212) 459-7483